American Journal of Medical Genetics (Neuropsychiatric Genetics) 67:354–360 (1996)

High Phenotypic Correlations Among Siblings With Autism and Pervasive Developmental Disorders

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The objective of this study was to examine familial factors influencing clinical variation in sibships that contained at least 2 children affected with autism or another form of pervasive developmental disorder (PDD). The sample included a total of 60 families, 23 with multiple cases of PDD and 37 with a single affected child. Measurements of IQ, adaptive behaviors in socialization and communication, and autistic symptoms were taken on all affected children. A high intraclass correlation, especially on IQ and an index of social behaviors, was observed between affected children from the same family. In contrast, low correlations were observed on measurements of IQ and adaptive behavior between affected and unaffected children from the same family. These data indicate that variation in severity of PDD is influenced by familial, and probably genetic, mechanisms. The results are discussed in relation to current theories on the genetics of autism and the heritable mechanisms underlying variations in clinical severity.

KEY WORDS: autism, genetics, family studies

INTRODUCTION

Autism is a developmental disability characterized by impairments in reciprocal social interaction in verbal and nonverbal communication, and by a pattern of repetitive, stereotypic activities. It represents one end of a spectrum of conditions termed "pervasive developmental disorders" (PDD) that share these clinical features but differ on natural history, number of symptoms, or pattern of behaviors [Szatmari, 1992]. Although it is clear that PDD has a neurological etiology, the precise location and nature of the deficit are unknown. About 10% of children with autism have an associated disorder of the central nervous system [Rutter et al., 1994]. Among the remaining "idiopathic" cases, family and twin studies have consistently demonstrated that genetic factors are important in the etiology of both autism and other forms of PDD [reviewed in Smalley, 1991; Szatmari and Mahoney, 1993]. However, the genetics of the disorder must be complex, since the pattern of expression in families does not follow simple Mendelian expectations. For example, the risk to siblings is between 3–5%, and there are about 4 affected boys to every affected girl [Smalley, 1991].

Enormous variability exists in the clinical expression of PDD, but the extent to which genetic or nongenetic factors account for this variability is currently unknown. Autism, which is characterized by lifelong disability, represents the most extreme form of PDD. IQ can range from "untestable" to above average, although high IQ is quite rare [Szatmari et al., 1990]. Similarly, about 50% of autistic children are mute, but many can have pedantic speech characterized by extreme talkativeness. Asperger disorder is a less severe form of PDD characterized by an absence of clinically significant language and cognitive delay [American Psychiatric Association, 1994]. Individuals with this form of PDD have much higher levels of adaptation and show improvement over time [Szatmari, 1992]. Atypical autism is another symptomatically milder form of PDD compared to autism, and affected individuals tend to be either very high-functioning or else quite developmentally delayed [Szatmari, 1992].

Several factors have been shown to be associated with this variability in clinical expression. For example, younger children and those with lower IQ tend to exhibit more severe symptoms and a greater degree of impairment [Bartak and Rutter, 1976]. Females with autism also tend to have lower IQ and, some reports suggest, a more severe form of the disorder than males [Tsai and Beisler, 1983], although this may be ex-

Received for publication May 18, 1995; revision received January 10, 1996.

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plained by differences in IQ [Volkmar et al., 1993]. Finally, there is some information on birth order. Lord [1992] presented data on a sample of multiplex (MPX) siblings with autism (i.e., families with more than one affected child). In these sibships, the second-born child tended to have a lower IQ than the firstborn. This potentially important finding has yet to be replicated.

Although we know that genetic factors are important in causing autism, previous studies have not examined whether such factors influence severity of clinical features. A convenient way to isolate genetic or familial factors influencing variable expressivity is to concentrate on MPX cases [Anderson et al., 1981]. These most likely represent "genetic" cases of autism and allow one to study in more detail the extent to which clinical variability is associated with a genetic etiology. This is best studied using twins, but such families are very rare. None of the published twin studies [Folstein and Rutter, 1977; Ritvo et al., 1985; Steffenburg et al., 1989] investigated whether concordant monozygous twins were more alike than concordant dizygous twins in severity of clinical features. Affected (nontwin) siblings, which are more common, can be used instead, although certain assumptions must be made. Evidence that a variable is influenced in important ways by familial factors is provided by demonstrating that a clinical characteristic shows little variability among affected children within a sibship, compared to affected children from different families. The main assumption is that this similarity is due to genetic factors as opposed to other environmental factors that may also be familial. However, since the familial aggregation of autism is largely accounted for by genetic factors (i.e., heritability appears to be over 90% based on prevalence of the disorder and differences in monozygous and dizygous concordance rates [Smalley, 1991; Plomin et al., 1994]), this may be a reasonably safe assumption.

The objective of this study was to assess, among MPX sibships, the variation within and between sibships in IQ, autistic symptoms, and measurements of adaptive behaviors in communication and socialization. These measurements provide separate but correlated indices of severity and variation in clinical expression. The intraclass correlation coefficient (ICC) was used to compare the variability within a sibship to that seen between sibships. ICC has been calculated for several measurements, since there is no single variable that captures all aspects of severity. Correlations in the MPX families have been compared with correlations between affected and unaffected children in sibships that contain a single affected PDD individual (so-called simplex (SPX) sibships). This was done to see if the observed correlations were specific to *affected* children in a family rather than to all children (regardless of PDD status).

MATERIALS AND METHODS

A sample of MPX families was recruited by several means. First, parents who were members of the Autism Society of Ontario were sent a questionnaire that enquired whether or not there was a second child in the family affected with autism, mental retardation, or PDD. Second, a letter was sent to all children's mental health and social service agencies in Southern Ontario that service children with developmental disabilities. Clinicians at these agencies were asked to fill out a brief form on any autistic or PDD child under their management, and to indicate whether or not the autistic/PDD child had a sibling with autism, PDD, or mental retardation. Third, a series of families with more than one child with PDD was identified from among those attending the PDD team at Chedoke-McMaster Hospitals.

Families with only one affected child with autism/PDD were also recruited for comparison purposes. Records at our facility were searched for all cases presently in treatment or assessment with a diagnosis of PDD. Families with a single affected male were matched to an MPX family on family size and age, so that male SPX families had as much chance of having multiply affected children as MPX families. This matching could not be done for the rarer female SPX families.

Once a child was identified as a potential "case," a clinical assessment was carried out on all children in the sibship to ascertain affected and unaffected children. All children were screened using parts of the Family History Interview for Developmental Disorders of Cognition and Social Functioning [Folstein and Rutter, 1991]. This interview asks parents whether their children displayed any PDD-like behaviors in their development. Children with a history of speech delay, social impairment, or restricted interests went on to have a fuller assessment involving a semistructured interview (the Autism Diagnostic Interview [Le Couteur et al., 1989]). This more detailed interview was administered to parents and covered details of developmental history, and systematically asked about impairments in reciprocal social interaction, verbal and nonverbal communication, and a range of repetitive and stereotypic activities. In addition, direct assessment of the child him/herself was conducted to assess social, language, and play skills (the Autism Diagnostic Observation Scale or ADOS [Lord et al., 1989]). Finally, clinical records were requested that contained information on diagnosis and clinical assessments. All this information was reviewed to make a diagnosis of autism or one of the other PDD subtypes (Asperger syndrome, disintegrative disorder of childhood, and atypical autism), according to the draft ICD-10 criteria [WHO, 1992]. A diagnosis of autism was made if the child demonstrated severe impairments in qualitative social interaction with parents and peers, deficits in verbal and nonverbal communication (including deviant language development), and a pattern of restrictive, repetitive behaviors. Asperger syndrome was diagnosed in children without clinically significant cognitive and language delay, but who still demonstrated qualitative impairments in reciprocal social interaction and a pattern of repetitive stereotypic behaviors. Atypical PDD was diagnosed when children demonstrated fewer behaviors in total than needed to receive a diagnosis of autism (no subject received this diagnosis if age of onset was over 3 years).

A proband was defined as the first child within a sibship to receive a diagnosis of autism or another PDD prior to the current assessment. If the proband re-

ceived a diagnosis of PDD by ICD-10 criteria, the following additional inclusion criteria were then applied: 1) age >4 years for the proband (this was considered the earliest age possible for a reliable diagnosis of PDD); 2) in SPX families, at least one unaffected sibling who could be assessed; 3) English as the language most often spoken at home; and 4) freedom from neurological disease or chromosomal disorder. All probands and affected siblings had extensive medical evaluations, including CAT scans, metabolic screens, EEGs, and chromosome testing to rule out known neurologic and chromosomal disorders.

Thirty-seven potential MPX families were identified and contacted. Eleven families did not wish to participate, and three sibships were ineligible because either one or both sibs were assessed as not having PDD or autism, leaving 23 families with 57 children. Diagnostic procedures were employed to diagnose 47 of these as affected with PDD (all but one family had 2 affected children), and 10 of these as unaffected children. We also recruited 18 families with a single affected male and 19 families with a single affected female. There were 33 unaffected sibs in each of these groups, respectively. We were able to obtain Vineland [Sparrow et al., 1984] data on 64 of 66 unaffected sibs, but IQ data on only 45 because of refusal to participate among sibs, geographic distance, or limited resources. The study was approved by the Research Advisory Committee of Chedoke-McMaster Hospitals.

Instruments and Measurements

Family history interview for developmental disorders of cognition and social dysfunction [Folstein and Rutter, 1991]. This is a semistructured interview that provides information on developmental disorders, social impairments, cognitive deficits, and psychiatric symptoms in children and adults. We employed only those sections of the interview that asked about developmental problems in order to screen for the presence of a PDD symptom in siblings.

Autism Diagnostic Interview (ADI) [Le Couteur et al., 1989] and Autism Diagnostic Observation Schedule (ADOS) [Lord et al., 1989]. The ADI is a semistructured interview conducted with parents, designed to make a diagnosis of autism according to both ICD-10 and DSM-III-R criteria. It systematically inquires about impairments in reciprocal social interaction, verbal and nonverbal communication, and a pattern of repetitive stereotypic activities both currently and at some point in development. The interview has good interrater and test-retest reliability and is able to correctly classify both autistic and developmentally-delayed children [Le Couteur et al., 1989]. Unfortunately, there is no algorithm to construct a diagnosis of Asperger syndrome or atypical autism from the ADI. As a result, we relied on the "best-estimate" approach to make a distinction among PDD subtypes.

ADOS is a direct assessment designed to make a diagnosis of PDD based on a 20-min structured observation. The examiner engages the child in nine separate activities designed to elicit behaviors specific to autism. ADOS also had good psychometric properties [Lord et al., 1989].

Intelligence measurements. Psychometric testing on probands and affected siblings was conducted with the Leiter Performance Scales [Levine, 1986] and other age-appropriate Wechsler intelligence tests [Wechsler, 1967, 1974, 1981]. All PDD children received the Leiter test. We also attempted to test all affected children with the WISC-R, WPPSI, or WAIS-R (depending on age), although some were unable to complete testing, particularly the verbal subtests. If a child was unable to complete the Leiter or Wechsler tests due to severe impairment in functioning, she/he was given a standard score 1 point below the lowest possible valid standard score obtained by another PDD child in the sample (i.e., 25 on the Leiter test and 33 on the WISC test). This was done to keep missing data to a minimum, and was felt to be a reasonably valid estimate of level of functioning.

Unaffected siblings were tested with the Stanford Binet (revised edition) IQ test [Thorndike et al., 1985]. The results reported here are from a larger study looking at the cognitive performance of all first-degree relatives of a large sample of PDD probands. The battery for the siblings was selected on the basis of sensitivity to verbal deficits, a finding previously reported in the siblings of autistic probands. PDD probands were not tested with the Stanford-Binet test because of their severe verbal deficits.

Vineland Adaptive Behavior Scales (VABS) [Sparrow et al., 1984]. VABS is also a semistructured interview administered to parents by a psychometrist. It is designed to measure adaptive behavior in the domains of socialization, communication, motor skills, and daily living skills. Communication and socialization scores, and their relation to other parameters such as IQ, are seen as very sensitive measures of impairment in PDD children [Volkmar et al., 1987]. A major advantage of the VABS is that the same instrument could be used with both affected children and their siblings for comparison purposes, and scores are adjusted for age differences.

Autism Behavior Checklist (ABC) [Krug et al., 1980]. These are checklists filled out by a parent, and they contain 57 items measuring a wide range of PDD symptoms within five scales: language, relating, body and object use, sensory stimulation, and social and self-help. Each item is scored as present or absent, and items can be weighted in order to arrive at both a subscale score and a total score. High scores reflect more "autistic" symptoms. This measure was taken only on affected children, since unaffected children were already shown to be free of autistic symptoms.

Analysis

To replicate the findings reported by Lord [1992], the first- and second-born PDD children in MPX families were compared, using a paired t-test to determine whether birth order affected clinical features. Most, but not all, probands were also the firstborn affected child in a family. The extent to which certain clinical features varied within, as opposed to between, sibships was investigated using the intraclass correlation coefficient (ICC). The IQ, VABS, and ABC scores were normally distributed in this sample, minimizing the effect of out-

liers on potential correlations. A high ICC indicated that affected siblings were more similar on clinical measurements than affected children from different families. The correlation in IQ between affected and unaffected children in the same families was assessed using Pearson correlations. Pearson correlations were used in this instance because there was a clear distinction between affected and unaffected children. The scores of each unaffected child were paired to his/her affected sibling, and a simple correlation was then run on these scores. Unaffected siblings from MPX families were excluded from this latter analysis, since of the 10 unaffected children, complete data were available on only 7.

RESULTS

To date, 23 families have been identified with multiple cases of autism/PDD. These families contain 47 affected children with PDD (i.e., only one family has more than 2 affected children) and 10 unaffected siblings. There are 21 male and 2 female probands, with 22 male and 2 female affected siblings. Paired t-tests comparing first- and second-born affected children indicate that there were no birth-order effects for any of these measurements (except, of course, for age). Mean ages of the first- and second-born affected children were 174.5 months (SD, 107.8) and 142.7 months (SD, 94.8), respectively. Mean IQ according to the Leiter test was 61.3 (SD, 34.4) for the firstborn and 65.2 (SD, 29.6) for the second-born ($t = -.67$, $df = 23$, P = ns). First- and second-born sibs were similarly impaired on the VABS socialization test (51.0, SD, 28.9 vs. 49.8, SD, 17.9, $t = .27$, $df = 22$, P = ns), VABS communication scales (53.3, SD, 33.0 vs. 53.0, SD, 24.3, $t = .06$, $df = 22$, P = ns), and the ABC tests (69.0, SD, 37.5 vs. 71.6, SD, 28.0, $t = -.31$, $df = 21$, P = ns).

Table I illustrates the large variability between MPX sibships in the clinical indices. Leiter IQ scores ranged from 25–143 in the probands. Similarly, among affected siblings, IQ ranged from 32–111, indicating a high degree of variability between PDD children in IQ. The next question was as to whether similar variability exists within MPX sibships. Although one sibship had a difference in Leiter IQ scores of 86 points between affected children, the mean difference in IQ between affected children from the same sibship was 19.3 IQ points (regardless of who had the higher score). The intraclass correlation for IQ was 0.62 ($P < .001$), indicating that nonverbal IQ from the Leiter test was similar among affected children from the same sibship, even in the context of the variation between sibships. The ICC using the WISC data (not shown) depended on the construct measured. The ICC for verbal IQ was 0.37 ($P < .03$), whereas the ICC for performance IQ was 0.75 ($P < .001$), and for full scale IQ was 0.53 ($P = .003$). Thus, the correlation among cognitive abilities was much higher for nonverbal measures than for the verbal Wechsler measurements.

Similar results were obtained for the other clinical measurements as well. Among the MPX affected children (proband and affected sibling), the mean VABS socialization score was 51.1 (SD, 23.6), with a range of 19–107. Within a sibship, the mean difference in socialization score was only 16.6 points, and the ICC for the Vineland socialization score was 0.62 ($P < .001$). For the VABS communication score, virtually identical results were obtained in terms of the mean (53.8), standard deviation (28.7), range (19–132), and mean difference in scores (19.9). In this instance, the ICC of 0.54 was slightly lower ($P = .003$). The mean score on the ABC test was 69.5 (SD, 32.5) with a range of 5–136. The mean difference in ABC score between affected siblings from the same family was 32.9 points, and the ICC was .30 ($P = .08$). All but one of these ICCs were highly statistically significant, with the ICCs on IQ and socializa-

TABLE I. Clinical Data on MPX Sibships

Family ID	Status[a]	IQ[b]	COM[c]	SOC[d]	ABC[e]
1	1	89	56	47	104
1	2	96	57	55	46
2	2	98	75	65	75
2	1	86	82	42	136
3	1	108	52	78	64
3	2	94	65	71	43
4	2	111	89	49	—
4	1	25	19	19	63
5	1	75	75	85	23
5	2	72	60	53	85
6	1	25	19	19	81
6	2	25	19	19	33
7	1	53	55	64	129
7	2	87	89	70	102
8	1	25	19	19	76
8	2	74	24	32	103
9	1	59	95	58	76
9	2	70	103	68	62
10	1	82	89	81	5
10	2	40	36	32	45
11	1	43	19	19	64
11	2	34	19	19	83
12	1	86	42	55	87
12	2	63	66	56	60
13	1	26	22	22	113
13	2	67	57	50	114
14	1	114	104	107	8
14	2	88	71	83	37
15	1	26	—	—	75
15	2	25	—	—	64
17	1	42	37	50	20
17	2	32	28	45	37
18	1	39	30	32	—
18	2	32	34	49	—
19	1	98	85	81	36
19	2	92	54	57	111
20	1	91	74	87	22
20	2	98	48	47	88
21	2	25	19	19	103
21	1	32	19	19	63
22	1	40	25	19	98
22	2	67	51	38	83
22	2	44	30	41	112
23	1	25	51	62	58
23	2	25	47	51	51
57	1	143	132	89	83
57	2	105	77	76	39

[a] 1, proband; 2, affected sibling.
[b] According to Leiter test.
[c] Vineland communication score (parent).
[d] Vineland socialization score (parent).
[e] ABC, Autism Behavior Checklist.

tion measurements as the highest of the indices. Thus, in spite of the fact that there was considerable variation among sibships in clinical severity, children with PDD from the same family were similarly affected.

There were 66 unaffected siblings in SPX families (26 males and 40 females). The mean Stanford-Binet IQ, VABS communication, and socialization scores in the unaffected siblings were 109.5 (SD, 10.8), 100.7 (SD, 14.7), and 98.4 (SD, 18.5), respectively, all scores well within normal range. Pearson correlations were computed to see if variations in sibling IQ across families was associated with proband IQ. Among all SPX families, the correlation for IQ between PDD children and their unaffected siblings (n = 24 sibships and 45 unaffected siblings) was $r = .23$ (P = ns). This indicates that familial factors affecting IQ in normal siblings did not influence IQ in the affected children. Similarly, the correlation between affected and unaffected siblings was $r = .10$ for the VABS communication scale and $r = .16$ for the socialization scale (both P = ns). The ABC scales were not completed on the unaffected siblings since they would naturally show little or no variation on this measure in the first place. Thus there was no correlation in clinical indices between affected and unaffected children from the same family.

DISCUSSION

The main finding of this study is that although there is considerable variation in the severity of clinical features and IQ among children with PDD, within a sibship, there was a remarkable degree of similarity among affected siblings. In fact, ICCs were higher than we had expected, particularly in view of the measurement error in IQ and adaptive behavior scores at the lower end of normal distribution. A high correlation was not seen between affected and unaffected siblings from the same family, and this cannot be explained by the usual factors that affect variation in IQ in families without PDD children. These findings suggest that familial, rather than nonshared environmental, factors account for variations in severity among affected PDD children from different families.

Similar data are available from three other studies, although they have not been analyzed in this way [Lord, 1992; Spiker et al., 1994; Ritvo et al., 1989]. In contrast to the findings reported by Lord [1992], we did not find an effect for birth order. In view of the systematic differences between affected siblings in her data, it is not surprising that the ICC for IQ (0.03) was much lower than in ours. Her set of 16 families was different from ours in terms of sex ratio (28 males and 5 females) and the fact that the mean IQ of the first affected child in her data was 76, higher than is usually reported for autistic children. This suggests that her sample may be unrepresentative of autistic/PDD children in general. Among the sibships in that data set where the firstborn had an IQ above 76, all 8 second-born children had a lower IQ. The pattern is not so clear among sibships where the firstborn's IQ was below the median; in three of eight pairs the later-born children had, in fact, higher IQs than the firstborn. Indeed, in our data set, when the firstborn PDD child had an IQ above 76, 6 of 8 second-born children also had lower IQ. In other words, the birth-order effect in Lord's data may be accounted for by the chance sampling of a set of firstborn PDD children with unusually high IQ. Moreover, if different tests were used to measure IQ at various ages, this would introduce an extra source of variation to the ICC in Lord's study.

A more extensive analysis was recently published by Spiker et al. [1994] on their set of 37 MPX families. They reported that there was little or no correlation among affected siblings on IQ. Although our sample and that of Spiker et al. [1994] are similar in terms of age, mean IQ, and ratio of affected to unaffected children, the sex ratio in their sample is closer to 1 than ours. In addition, they restricted their sample to children with autism, whereas we included those with atypical autism and Asperger syndrome, which would tend to increase variation among sibships. Finally, the IQ data used by Spiker et al. [1994] were obtained from medical records rather than in a standardized manner using a variety of different IQ tests and measurements (nonverbal IQ, performance IQ, and full-scale IQ) depending on the availability of data. This introduces an extra source of variation to the ICC, in addition to the observed variation among and within sibships. Furthermore, there is evidence in our data that the ICC for nonverbal IQ is higher than for verbal IQ. Thus, both the sample and the measurements are different from ours and may explain the discrepant results.

Ritvo et al. [1989] described a sample of multiple-incidence families from Utah, and found an ICC for IQ of 0.68 (unpublished data based on 20 sibships with 46 affected children), very similar to our estimates. Moreover, Freeman et al. [1989] reported no significant correlation in IQ between unaffected first-degree relatives and autistic probands in this same sample. It can be inferred that the correlations must have been below .15 in light of the large sample size and the lack of statistical significance. It seems that as long as a uniform measure of nonverbal IQ is used and variation due to differences in age is eliminated, a high phenotypic correlation is observed between autistic/PDD siblings.

These data may have implications for the genetics of the disorder. One possibility is that a genetic maternal effect may account for the high phenotypic correlation observed between affected siblings. For example, children of mothers with phenylketonuria often have developmental delays and congenital anomalies due to circulating levels of phenylalanine in their bloodstream [Levy and Waisbren, 1983]. Two children from the same family are often affected to the same degree, depending on the level of maternal phenylalanine. Although there is little evidence for a maternal effect in autism/PDD, we have reported four cases of PDD among the *maternal* relatives of autistic/PDD probands [Szatmari et al., 1995]. Such a pattern is not inconsistent with a genetic maternal effect, and could be explored more fully.

Another possibility is that the mutation causing autism/PDD is unstable or dynamic. This type of genetic defect has recently been described in several neurologic disorders, including fragile X and E syndromes [Knight et al., 1994], spinal muscular atrophy,

myotonic dystrophy [Harley et al., 1992], Huntington's disease [Huntington's Disease Collaborative Research Group, 1993], and, most recently, dentatorubral-pallidoluysian atrophy [Koide et al., 1994] and Machado-Joseph disease [Kawaguchi et al., 1994]. The mechanism of mutation in these conditions is an expansion of trinucleotide repeat (TNR) sequences of DNA. These disorders are transmitted in a dominant fashion and are characterized by imprinting, anticipation, and a large variation in clinical features among families but little variation within families. The number of repeats usually correlates with some aspect of clinical expression. For example, the number of repeats in fragile X syndrome correlates with cytogenetic expression of fragile sites, anthropomorphic measurements, and degree of mental retardation [Rousseau et al., 1994]. Similarly, the number of repeats in the Huntington disease gene correlates with age of onset and age of death [Andrew et al., 1993]. Of particular interest with respect to the results reported in our study is the correlation between affected siblings in these conditions. Before the discovery of the FMR-1 gene, Fisch et al. [1991] reported that the correlation in cytogenetic expression of cells with fragile sites between affected siblings with fragile X syndrome was 0.26 (or between .18–.61, depending on the laboratory). Similarly, in Huntington's disease, the correlation in TNR repeats between affected siblings is .63 when the mutation is inherited from the father, and 0.90 for maternal transmission [Snell et al., 1993].

A similar process of TNR expansion could occur in autism/PDD; different families would have different numbers of repeats, explaining the variation among families, but affected siblings from the same family would have similar numbers of repeats and be affected to a similar degree. The correlations we obtained based on purely clinical measures are consistent with those seen in TNR disorders, which are based on direct DNA assessments and cytogenetic expression of fragile sites.

The possibility of unstable mutations could explain the variable expressivity in autism/PDD and other puzzling findings in the genetics of autism, including the low recurrence risk to siblings and other collateral relatives [Szatmari et al., 1995], the stable prevalence of the disorder in spite of being genetically lethal [Wing and Gould, 1979; Bryson et al., 1988], and the often-reported finding that parents, and particularly fathers, have mild social impairments reminiscent of PDD that would not meet the full criteria for the disorder [Narayan et al., 1990; Landa et al., 1992]. Further genetic studies will be needed to explore these possibilities in more detail.

This study has some limitations that should be kept in mind. First, the number of MPX families is quite small, making analyses of more specific subgroups difficult. For example, it would be interesting to see if the sex of the proband or the PDD subtype of either affected individual (e.g., Asperger syndrome vs. autism) makes a difference to the ICC. Second, it is unfortunate that we had to use different IQ tests on the affected and unaffected children. However, the IQ results we obtained were replicated by the results on the VABS, where identical measures were used. Third, the VABS and ABC data were based on parental report, which might inflate intrafamily similarity. However, the highest ICC was seen for IQ, which is assessed independently. Fourth, without a sample of twins we cannot determine whether the high ICC is due to genetic or environmental reasons. We would argue, however, that in view of the high heritability seen in autism and the fact that no environmental factors responsible for familial aggregation have been identified consistently, it is a reasonable assumption that genetic factors account for the greatest proportion of similarity between affected siblings [Plomin et al., 1994].

As far as we are aware, the results reported here are the first indication that the considerable variation in clinical features in PDD is under familial, and presumably genetic, control. Severity of impairment in measures of social-communication development, nonverbal IQ, and autistic symptoms appears to be genetically determined. An intriguing possibility is that a maternal effect or unstable mutation may be responsible for this correlation among affected siblings along with many of the other features of this disorder. Indeed, unstable mutations may be a feature of several complex genetic disorders that were previously considered to be caused by polygenic-multifactorial mechanisms [Ross et al., 1993]. More importantly, the findings reported here may lead to other testable hypotheses, that may in turn provide further insights into the etiology of autism.

ACKNOWLEDGMENTS

This work was supported by a grant from the Medical Research Council of Canada. We thank all the children and families that participated, and Dr. Ed Ritvo for access to data from his studies.

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